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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,617	07/27/2000	Laure Dumoutier	LUD 5664 US	9662

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/626,617	DUMOUTIER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/25/04

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application. 1-12, 22-32

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1-12, 22-32

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 2/25/04, has been entered.

Claims 1-12 and 22-32 are pending and being acted upon presently.

Claims 13-21 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 2/25/04.
The rejections of record can be found in the previous Office Action.

3. It appears that the instant claims have the benefit under 35 U.S.C. § 120 to the instant application USSN 09/626,617, filed 7/27/00. It does not appear to the previous priority USSNs support the instant claims, particularly as it relates to "IL-TIF/IL-21".

Again, If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the parent application. Applicant is reminded that priority relies upon written support and enablement under 35 USC 112, first paragraph, for the instant claims.

In addition to the rejections under 35 USC 112, first and second, paragraphs set forth herein, it is noted that the term "IL-TIF/IL-21" may have been renamed "IL-22" by the appropriate authorities and acknowledged by the coinventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1).

Applicant's statement, filed 2/24/04, that relevant administrative authorities and not inventors have rename the molecule is acknowledged.

4. Claims 1-12 and 22-32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification,
while enabling for an in vitro method of stimulating expression of STAT3 and STAT1 comprising contacting a hepatoma cell capable of said expression with an amount of human IL-TIF/IL-21 encoded by SEQ ID NOS 24/25;
while enabling for an in vitro method of stimulating expression of STAT3 and STAT5 comprising contacting a cell selected from the group of mesangial, neuronal melanoma and hepatoma cells capable of said expression with an amount of mouse IL-TIF/IL-21 encoded by SEQ ID NOS: 7/9;
does not reasonably providing enablement for the broader recitation of
a method for stimulating expression of any STAT transcription factor,
a method of contacting any cell capable of said expression with an amount of any IL-TIF/IL-21, including methods of treatment.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 2/24/04, have been fully considered but are not found convincing essentially for the reasons of record.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

A) Scope of IL-TIF/IL-21s, STATs and Cell Targets.

While applicant admits that the specification discloses that not all cells do in fact produce STAT-3 when stimulated, applicant asserts that the claims require that the stimulated cells be those capable of expressing STAT3 and that it would not require undue experimentation to identify relevant cells.

The instant claims are drawn broadly to contacting cells with any IL-TIF/IL-21, including any mammalian IL-TIF/IL-21. However, the instant specification does not enable any IL-TIF/IL-21 or the scope of IL-TIF/IL-21 broadly encompassed by the claimed invention.

It is noted that the claimed IL-TIF/IL-21 proteins include IL-TIF/IL-21 from other animal species, including other mammals as part of the invention (see page 35, lines 1-3 of the instant specification).

Further, it is noted that the claimed IL-TIF/IL-21 proteins range from about 17-22 kD as determined by SDS-PAGE, which activate STAT proteins and in glycosylated form, these proteins range from 17 to about 30 kD, as determined by SDS-PAGE (see page 36, paragraph 3 of the instant specification).

Proteins encoded by the disclosed nucleic acids encompass immediate products of nucleic acid expression, glycosylated forms and multimeric forms comprising at least one protein of the invention or at least one different protein (see page 36, paragraph 1 of the instant specification).

Applicant has not disclosed an isolated nucleic acid molecule which encodes a T cell inducible factor (TIF) which activates STAT, including STAT 3, as recited in the instant claims, other than IL-TIF/IL-21 encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

Neither has applicant disclosed the structural basis or nexus for activation of STAT 3 by the T cell derived inducible factor (TIF) encoded by the disclosed nucleic acids consisting of cDNA and genomic sequences of TIF.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any mammalian "IL-TIF/IL-21". "IL-TIF/IL-21" may have some notion of the function of the protein, however, there is insufficient guidance and direction as how to make and use the claimed genus of "IL-TIF and IL-21" commensurate in scope with the claimed methods. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "IL-TIF or IL-21" in the claimed methods to stimulate STAT transcription factors or acute phase proteins in a cell.

For example, the specification discloses a diversity of structure and function of the disclosed IL-TIF/IL-21 encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

Although the instant specification discloses high homology between mouse TIF alpha and beta (and therefore hybridizes to mouse TIF alpha under stringent conditions), there is insufficient guidance and direction as to critical common structural elements that define a IL-TIF/IL-21 or that define a T cell inducible factor alpha or beta and, in turn, the nexus between structure in an IL-TIF/IL-21 and its ability to stimulate the expression of STAT, including STAT 3.

IL-TIF/IL-21 does not bind STAT, including STAT 3, that is, they are not related as a ligand-receptor binding pair.

Applicant is not sure about the relevance concerning the issue that IL-TIF/IL-21 does not bind STAT, including STAT 3, that is, they are not related as a ligand-receptor binding pair.

As indicated previously, the prior art as well as the specification describe a diversity of structure and function of the disclosed IL-TIF/IL-21 encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

The claims rely upon the indirect stimulation of STAT 3 transcription factor by contacting cells with an amount of IL-TIF/IL-21. It would seem likely that the indirect nature of the relationship between STAT 3 transcription factor and IL-TIF/IL-21 contributes to the complexity and lack of predictability of the biological activities of one IL-TIF to another as well as from one system (e.g., in vitro, cell type) to another and, in turn, of extrapolating from the limited disclosure to the breadth of the claims is contributed.

For example as pointed out previously, the co-inventors have disclosed that the biological activities of IL-TIF remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse IL-TIF, IL-TIF does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, this reference distinguishes mouse from human IL-TIF as well as from in vitro and in vivo studies of IL-TIF (see Discussion). This discrepancy between in vitro and in vivo IL-TIF induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating TIF-IL (see Discussion).

Consistent with the Examples in the instant specification (e.g. Examples 21 and 27), it is noted that the co-inventors have published the same or similar results disclosed in the specification as filed. For example, see Dumoutier et al. PNAS 97: 10144-10149, 2000 and Dumoutier et al., J. Immunol. 164: 1814-1819, 2000.

This referenced distinction between IL-9 and TIF-IL differs from the instant disclosure which states that IL-TIF/IL-21 is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

The co-inventors have disclosed that the mouse IL-TIF was found to induce to STAT 3 and 5 activation in mesangial and neuronal cell lines but failed to reproduce activities such as the induction of proliferation of T helper clones, mast cells or inhibition of corticoid-induce apoptosis (Dumoutier et al., J. Immunol. 164: 1814-1819, 2000; see entire document, including Abstract and Discussion) (also see Example 21 of the instant specification).

In contrast to mouse IL-TIF, human IL-TIF induced STAT 1 and 3 in human hepatoma cells (see (Dumoutier et al. PNAS 97: 10144-10149, 2000) (See Example 27 of the instant specification).

It is noted that the starting material of peripheral blood cells for human TIF was stimulated with anti-CD3 antibodies and not IL-9 (see page 23, paragraph 1 of the instant specification). Anti-CD3 antibodies can stimulate a variety of molecules and are not limited to stimulating TIF alpha or beta. The instant specification further discloses that TIF mRNA can be expressed in the absence of IL-9 (see Example 14, particularly page 17, lines 4-5 of the instant specification.

While applicant asserts that failure to upregulate in vivo simply reflects possible need for preactivation by stimuli, such as antigenic or inflammatory stimuli.

However, there is no evidence of this assertion by applicant, the claims do not reflect this preactivation step and the specification as filed does not appear to provide recognition of this asserted critical element for in vivo administration.

In addition, it is noted that the term "IL-TIF/IL-21" may have been renamed "IL-22" by the administrative authories and acknowledged by the coinventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1). Here, it is noted that the coinventors have shown that the signaling pathways associated with IL-22 were not the same as IL-10, as previously thought (see entire document, including page 1, column 2, paragraph 2).

With respect to applicant assertions that the following is a series of unrelated comments, it is noted that the following comments and evidence were set forth to indicate that applicant should amend the claims to limit the claims to the use of human IL-TIF/IL-21 encoded by SEQ ID NOS 24/25 or mouse IL-TIF/IL-21 encoded by SEQ ID NOS: 7/9. Applicant has not disclosed an isolated nucleic acid molecule which encodes a T cell inducible factor (TIF) which activates STAT, including STAT 3, as recited in the instant claims, other than IL-TIF/IL-21 encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

The following of record provides evidence to support the lack of predictability of a genus of IL-TIF/IL-21 based upon a limited number of species, including reliance on sequence homology or encompassing a genus wherein the amino acid structure of a protein is subject to modification.

As pointed out previously and above, the instant claims are drawn broadly to contacting cells with any IL-TIF/IL-21, including any mammalian IL-TIF/IL-21. However, the instant specification does not enable any IL-TIF/IL-21 or the scope of IL-TIF/IL-21 broadly encompassed by the claimed invention.

It is noted that the claimed IL-TIF/IL-21 proteins include IL-TIF/IL-21 from other animal species, including other mammals as part of the invention (see page 35, lines 1-3 of the instant specification).

Further, it is noted that the claimed IL-TIF/IL-21 proteins range from about 17-22 kD as determined by SDS-PAGE, which activate STAT proteins and in glycosylated form, these proteins range from 17 to about 30 kD, as determined by SDS-PAGE (see page 36, paragraph 3 of the instant specification).

Proteins encoded by the disclosed nucleic acids encompass immediate products of nucleic acid expression, glycosylated forms and multimeric forms comprising at least one protein of the invention or at least one different protein (see page 36, paragraph 1 of the instant specification).

The following of record is reiterated for applicant's convenience.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Applicant is relying upon certain biological activities and the disclosure of this limited number of mouse and human IL-TIF species to support an entire genus of IL-TIF/IL-21. Yet the instant specification does not provide sufficient guidance and direction how to make and use any "IL-TIF /IL-21", as encompassed by the claims. Also, the specification does not provide for the correlation or nexus between the chemical structure and the function of the genus of "IL-TIF / IL-21", currently encompassed by the claimed invention. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. IL-TIF/IL-21) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a limited number of IL-TIF sequences from mouse and human and in turn utilizing predicted structural determinations to ascertain functional aspects of the genus of IL-TIF / IL-21 proteins and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead the skilled artisan to make and use the genus of IL-TIF/IL-21 in the claimed methods other than those disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a IL-TIF/IL-21 encoding a functional IL-TIF/IL-21 structure as the relationship between structure-function was not well understood and was not predictable. Also, see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "IL-TIF/IL-21 employed in the claimed methods.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "IL-TIF/IL-21" other than those disclosed in the specification as filed (e.g. proteins encoded by SEQ ID NOS: 7, 8, 24, 25) as the agent in the claimed methods

It is acknowledged that the instant specification does describe methods for screening and evaluating nucleic acid molecules that encode nucleic acid molecules which encode IL-TIF/IL-21, which also induce STAT3.

However, the instant application does not provide the necessary link between these steps of screening and evaluating nucleic acids encoding IL-TIFs. There is insufficient guidance in the way of selecting an IL-TIF without the need of undue experimentation. The instant application provides assays for determining whether a nucleic acid encodes a protein with certain desired characteristics (e.g. activates STAT3) and identifies certain specific IL-TIFs from two mammalian species (mouse and human).

These descriptions without more precise guidelines amount to little more than a starting point, a direction for further research. The specification provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement for the scope of the claimed IL-TIF/IL-21 employed in the claimed methods.

Neither the specification nor the prior art provides a structural basis for the recited activity of the encoded protein. Without such guidance, predicting the structure that defines a TIF-IL/TIF-21 other than those IL-TIF/IL-21 encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25, and which possesses the claimed biological activities of stimulating STAT activation or acute phase production (other than an IL-TIF/ IL-21 encoded by nucleic acid molecule consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25), is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). In re Fisher, 166 USPQ 19, 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Therefore, there is insufficient evidence of record to show that one skilled in the art would be able to practice the scope of the claimed invention as claimed without an undue amount of experimentation.

B) In Vitro versus In Vivo.

The specification does not adequately teach how to effectively treat any disease or reach a therapeutic endpoint in humans by administering IL-TIF/IL-21, including subjects suffering from lymphoma, an immune system disorder such as an allergy, AIDS, autoimmune diabetes, thyroiditis (e.g. see pages 38-41 of the instant specification). The specification does not teach how to extrapolate data obtained from in vitro assays of contacting certain cell types with mouse and human IL-TIF/IL-21 under defined culture conditions (Examples 21 and 27) or the ability of mouse IL-TIF to induce certain acute phase proteins in an experimental mouse model (Examples 31-32) to the development of effective in vivo human therapeutic methods of inducing STAT expression or acute phase proteins in vivo, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of administering the claimed IL-TIF/IL-21 exemplified in certain experimental conditions disclosed in the specification to the methods encompassed by the claimed methods.

While applicant asserts that failure to upregulate in vivo simply reflects possible need for preactivation by stimuli, such as antigenic or inflammatory stimuli.

However, there is no evidence of this assertion by applicant, the claims do not reflect this preactivation step and the specification as filed does not appear to provide recognition of this asserted critical element for in vivo administration.

The following of record is reiterated for applicant's convenience.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental models accurately reflects the relative efficacy of inducing STAT activation or acute phase proteins with IL-TIF/IL-21 in a therapeutic manner to treat subjects suffering from lymphoma, an immune system disorder such as an allergy, AIDS, autoimmune diabetes, thyroiditis (e.g. see pages 38-41 of the instant specification).

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

As pointed out above, there is a distinction between IL-9 and the IL-TIF/IL-21 both in vitro and in vivo. For example, see the Discussion of Dumoutier et al. PNAS 97: 10144-10149, 2000. This distinction between IL-9 and TIF-IL differs from the instant disclosure which states that IL-TIF/IL-21 is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

For example, the co-inventors have disclosed that the biological activities of IL-TIF remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse IL-TIF, IL-TIF does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, the reference distinguishes mouse from human IL-TIF as well as from in vitro and in vivo studies of IL-TIF (see Discussion). This discrepancy between in vitro and in vivo IL-TIF induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating IL-TIF (see Discussion).

This reported distinction between IL-9 and IL-TIF differs from the instant disclosure which states that IL-TIF/IL-21 is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

In addition, it is noted that the term "IL-TIF/IL-21" may have been renamed "IL-22" by the coninventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1). Here, it is noted that the coinventors have shown that the signaling pathways associated with IL-22 were not the same as IL-10, as previously thought (see entire document, including page 1, column 2, paragraph 2).

It is noted that Il-TIF/IL-21 upregulates the production of acute-phase reactants, such as serum amyloid A, alpha-1 anti-chymotrypsin and haptogloblin in hepatoma cells and a similar activity has been observed in vivo in BALB/c mice, where the serum amyloid A mRNA was increased.

However upon the administration of an adenovirus encoding IL-TIF/IL-22 or IL-22 in C57BL/6 mice, the prolonged IL-TIF/IL-22 expression led to decreased red blood cell count, increased platelet count, decreased serum albumin and increased serum amyloid A and fibrinogen and decreased body weight (see Pittman, Genes Immun. 2: 172, 2001; Abstract).

Karras (U.S. Patent No. 6,159,694) discloses that in order to treat inflammatory diseases and cancer, the skilled artisan would have inhibited STAT3 expression in the treatment of inflammatory diseases and cancer (see Background of the Invention).

Therefore, it appears an inconsistency between the instant disclosure to treat subjects suffering from lymphoma, an immune system disorder such as an allergy, AIDS, autoimmune diabetes, thyroiditis (e.g. see pages 38-41 of the instant specification) and the instant claims which are drawn to stimulating STAT3 and acute phase proteins.

There is insufficient predictability in applying a nexus with the experimental results of administering IL-TIF/IL-21 (or IL-22) either in vitro or in vivo and the expectation by the skilled artisan that the treatment of cancer and inflammatory diseases would have been treated with antagonists rather than agonists of STAT with the instant disclosure to inhibit STAT3 in the treatment of cancer and inflammatory diseases with the instant disclosure to therapeutic regimens to treat subjects suffering from lymphoma, an immune system disorder such as an allergy, AIDS, autoimmune diabetes, thyroiditis (e.g. see pages 38-41 of the instant specification).

It has been well known that cytokines are proteins that exert their action by binding to specific cell surface receptors, leading to activation of cytokine-specific signal transduction pathways. Cytokines can exhibit pleiotropic activity within and outside the immune system. Cytokines, cytokine receptors and antibodies thereto can act both as potentiation and inhibitory agents, depending upon the site and timing of exposure as well as the nature of the particular model or therapeutic setting.

Given the pleiotropic effects of factors or cytokines; there are distinct differences in the role that cytokines play in different types of inflammation or diseases and, in turn, there would have been unpredictability in treating various neoplastic and inflammatory conditions encompassed by the claimed invention and disclosed in the specification as filed.

Given the interactive and complicated regulatory mechanisms associated with cytokines in general as well as with IL-TIF/IL-21 as well as the experimental results associated with IL-TIF/IL-21, there is insufficient guidance and direction in the specification as filed to how to induce STAT activation or acute phase proteins with IL-TIF/IL-21 in a therapeutic manner to treat subjects suffering from lymphoma, an immune system disorder such as an allergy, AIDS, autoimmune diabetes, thyroiditis as disclosed by the instant specification as filed (e.g. see pages 38-41 of the instant specification). There is insufficient direction and guidance in the specification to teach the skilled artisan how to use the claimed methods in a practical manner in vivo.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective induction of acute phase proteins and STAT activation in therapeutic regimens in humans, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating neoplastic or inflammatory conditions.

Applicant's arguments have not been found persuasive.

5. Claims 1-12 and 22-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 and 22-32 stand indefinite in the recitation of "IL-TIF/IL-21" in that they only describe the products of interest employed in the claimed methods by an arbitrary protein name. While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. Applicant should particularly point out and distinctly claim the "IL-TIF/IL-21" by claiming sufficient characteristics associated with the protein (e.g. amino acid or nucleic acid sequence). Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of.

In addition, it is noted that the term "IL-TIF/IL-21" may have been renamed "IL-22" by the appropriate authorities (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1).

Furthermore, Ebert notes confusion and ambiguities in labeling cytokines as interleukins, including IL-TIF/ IL-21 (Trends in Immunology 23: 341-342, 2002).

Applicant should specifically point out the support for any amendments made to the disclosure.

See MPEP 714.02 and 2163.06

6. Claims 1-12 and 13-21 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Ebner et al. (US 2003/0003545 A1) (see entire document) as further evidenced by Renauld et al., US 2003/0012788 A1), which discloses that the instant T cell inducible factor has been named "IL-TIF/IL-21" and, in turn, has been renamed "IL-22" (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1).

Applicant arguments in conjunction with the Dumoutier / Renauld declaration under 37 C.F.R. § 1.131, filed 2/2104, have been fully considered but are not found convincing as it applies to Ebner (U.S. 2003/0003545 A1)

The 1.131 affidavit is deficient because:

(a) the declaration indicates that the the claimed subject matter was reduced to practice no later than May 27, 1999, while Ebner et al. has U.S. priority dates of 5/29/98, 9/10/98 and 4/30/99. Therefore, the declaration does not antedate the prior art reference.

(b) it is not readily apparent that the experiments set forth in the declaration and relate back to Example 21 of the instant specification encompasses the contacting of a cell capable of said expression with an amount of an IL-TIF/IL--21 sufficient to stimulate said expression. For example, it is not clear what was administered to said cells. While the evidence is in French and not English, it appears that the cells may have been exposed to sense and antisense nucleic acids and not IL-TIF/IL-21. Measuring the stimulation of STAT 3 and STAT 5 transcription factors in the Exhibits is not readily apparent.

Applicant is invited to provide more details concerning the actual methods relied upon applicant in the 1.131 Declaration. It is the responsibility of the declarant to clearly explain the documentary exhibits and indicate that these exhibits are intended to evidence in addition to the averment of the acts which he is relying upon. See In re Borkowski and Van Venrooy 184 USPQ 29 (CCPA 1974). The exhibits attached to the declaration are not themselves and entirely self-explanatory and the declarant has provided insufficient explanation of the exhibits.

(c) the declaration does not appear to provide sufficient evidence to antedate the scope of the prior art teaching as it reads on the breadth of the claimed methods, including
Also, the claims are broader and the prior art is broader than

The following of record is reiterated herein for applicant's convenience.

Ebner et al. teach the administration IL-21 and IL-22 polypeptides to replace absent or decreased levels of the IL-21 and IL-22 polypeptides, respectively, to supplement absent or decreased levels of a different polypeptide, to inhibit the activity of a polypeptide, to activate the activity of a polypeptide, to reduce the activity of a membrane bound receptor or to bring about a desired response (see page 35, column 1, paragraph 2 and Example 25 on page 55).

In addition, Ebner et al. teach the signal transduction pathway involved in the differentiation and proliferation of cells, including the presence of STAT 3 and STAT 5 in cells upon activation (see Example 12 on pages 46-47). Examples 13, 14 and 15 are drawn to screening assays of T cell, myeloid and neuronal activity with IL-21/IL-22 to determine the expression transcription factors, including STAT3 (see pages 46-50).

Although the reference does not disclose acute phase proteins such as human serum amyloid A, chymotrypsin or haptoglobin as well as liver cells per se, these claimed functional limitations would be inherent properties of the referenced methods to administer IL-21/IL-22 in an individual.

Further, the instant T cell inducible factor has named "IL-TIF/IL-21" and, in turn, has been renamed "IL-22" by the appropriate authorties and acknowledged by the coinventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1).

Applicant's arguments in conjunction with the 1.131 Declaration have not been found persuasive.

7. No claim allowed.

8. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 9, 2004